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# Wheeze in children: the impact of parental education on atopic and non-atopic symptoms

de Meer G, Reijneveld SA, Brunekreef B. Wheeze in children: the impact of parental education on atopic and non-atopic symptoms. *Pediatr Allergy Immunol* 2010; 21: 823–830.

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There is conflicting evidence for the relationship between parental socioeconomic position and their children's asthma. The aim of this study was to investigate relationships between parental education and respiratory symptoms in their children, distinguishing atopic and non-atopic symptoms. A cross-sectional survey among 3262 elementary school children (age 8–13) was performed; data on parental education were obtained for 3213 children. Parents completed a questionnaire on their child's allergic and respiratory symptoms, and potential explanatory variables including family history, indoor environment, and the child's medical history. Subsets of children were tested for atopy ( $n = 1983$ ), lung function ( $n = 2325$ ), and airway hyperresponsiveness (AHR) ( $n = 880$ ). Logistic regression was used to assess relationships of health outcomes with parental education. A high parental education was associated with an increased risk of atopic sensitization to indoor allergens (OR 1.31, 95% CI 1.02; 1.69). Studied explanatory variables did not influence the relationship. In contrast, a high parental education protected children from wheeze (OR 0.77, 95% CI 0.61; 0.97). This only applied to non-atopic wheeze (OR 0.65, 95% CI 0.43; 0.99) and not to atopic wheeze (OR 0.89, 95% CI 0.60; 1.31). The protection from non-atopic wheeze in children of highly educated parents declined after adjustment for household smoking and breastfeeding (OR 0.96, 95% CI 0.58; 1.57). Similar results were observed for non-atopic and atopic rhinitis. We conclude that children from highly educated parents are protected from non-atopic respiratory symptoms, which is largely explained by a lower rate of household smoking and a higher rate of breastfeeding.

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Key words: socioeconomic status; atopy; atopic asthma; non-atopic asthma; atopic rhinitis; non-atopic rhinitis; parental education

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Socioeconomically deprived groups are at risk of adverse health due to unhealthy life styles, material deprivation and psychosocial stress (1–6). Asthma prevalence rates have increased over the past decades (7–11) though there seems some stabilization in recent surveys, especially in older children (12, 13). The ISAAC studies phase one and three provide valid figures of the change in prevalence rates between 1991 and 1999. In Western European countries, asthma prevalence

rates increased from 8.1 to 9.7% for 6–7 yrs old children, and were stable around 15% for 13–14 yrs old children.

Previous studies have consistently shown lower prevalence rates for atopy and eczema among individuals with a low socioeconomic position (14–16). For asthma, however, the pattern is less clear (17, 18). In recent years the distinction between allergic and non-allergic asthma has got more attention. For atopic asthma a parental

history of asthma is the most important risk factor, while for non-atopic asthma indoor air quality plays a dominant role (e.g. environmental tobacco smoke and home dampness) (19–21). It is commonly known that a low socioeconomic position is associated with adverse housing conditions including indoor smoking (6, 22). Therefore, the relationship of socioeconomic position with airway symptoms may depend upon a joint presence of atopy. So far, however, none of the studies on socioeconomic position and asthma distinguished between atopic and non-atopic wheeze phenotype.

The aim of this study was to investigate the relationship of parental socioeconomic position and childhood airway symptoms, distinguishing between atopic and non-atopic symptoms. In addition, we searched for environmental factors that explained observed relationships.

## Methods

### Study population and design

The population comprised 4626 school children (aged 7–13 yrs) that participated in two cross-sectional studies on respiratory health effects of traffic related air pollution. A detailed description has been published previously (23). In short, 30 elementary schools located within 400 m distance of a freeway were selected, of which 24 agreed to participate. Reasons for refusal were not related to the aim of the study (reorganization, involved in other studies, etc).

The study protocol included a parent-completed questionnaire, and the assessment of lung function, weight and height. Children aged 8 and over ( $n = 4111$ ) were invited for atopy testing, and participants of one of the studies ( $n = 2207$ ) were additionally invited for airway challenge testing. Parents needed to give permission for each test separately. The Medical Ethical Board of the University of Wageningen approved of the study protocol.

For this paper we restricted the population to children invited for atopy testing ( $n = 4111$ ), and excluded non-Dutch parents ( $n = 849$ ) to avoid ambiguity on parental education. Our data did not allow analysis on ethnic background since information on parental birth was limited to 'born in the Netherlands [yes/no]'. The final population included 3262 children.

### Parental education

Parental education was categorized into three levels using the highest completed educational

level for each parent as 'low' (lower vocational, i.e. max. 12 yrs), 'intermediate' (13–16 yrs), and 'high' (high vocational or university degree, i.e. 17 yrs or more).

### Symptoms

Parents completed the respiratory symptoms questionnaire of the International Study on Asthma and Allergies in Childhood (ISAAC) (24). 'Ever asthma' was defined by confirmation if the child ever had asthma. Symptoms of wheeze, rhinitis (a blocked or runny nose), and itchy rash were asked for occurrence in the past 12 months while not having a cold. Rhinconjunctivitis was considered if itchy eyes co-occurred with rhinitis symptoms.

### Atopy

Atopy was assessed by skin prick tests (SPT) and serum specific IgE. SPTs were performed using a panel of seven common allergens (ALK, Nienwegein, The Netherlands). Sera with a positive result in the Phadiatop were tested for specific IgE using CAP-assay (Pharmacia, Woerden, The Netherlands). Tested allergens included mixed grass pollen, mixed tree pollen, cat dander, dog dander, house dust mite, and moulds. Atopy was considered if either any SPT yielded a wheal diameter  $\geq 3$  mm, or specific IgE  $\geq 0.35$  kU/l.

### Lung function and airway hyperresponsiveness

Airway challenge with hypertonic saline (HS) was performed according to the protocol approved by the ISAAC steering committee. Salbutamol was withheld for 6 h, antihistamines and cromoglycate for 48 h. Children were excluded if baseline FEV<sub>1</sub> < 75% of the predicted value, or if unable to perform satisfactory forced spirometry maneuvers. HS aerosol was generated by an ultrasonic nebuliser in a closed system (Jaeger, Bilthoven, The Netherlands) with a mean output of 1.5 g/min which remained constant during the study period. Children inhaled for subsequently 0.5, 1, 2, 4 and 8 min (cumulative inhalation time 15.5 min, i.e. 23.0 g). After each dose step, two reproducible measurements of FEV<sub>1</sub> were achieved. The test stopped after 15.5 min cumulative inhalation time, or if FEV<sub>1</sub> fell with 15% or more compared to the baseline value. Salbutamol was administered if needed to relieve symptoms. The inhaled dose was determined by the weight difference of the HS containing canister prior

and after the challenge test. For tests with at least 15% fall in  $FEV_1$ , the dose needed for a 15% fall in  $FEV_1$  ( $PD_{15}$ ) was assessed by linear interpolation between the last two points in the dose-response curve. AHR was defined as a  $PD_{15} \leq 23.0$  g.

#### Potential explaining variables

Questionnaire data were collected on personal, family and living conditions. Personal conditions comprised the child's birth weight and gestational age, breastfeeding, and current overweight or obesity. A birth weight  $< 2500$  g was considered 'low birth weight', and prematurity if the child was born at a gestational age  $< 37$  wks. Overweight and obesity were defined according to age and sex-specific international standards equivalent to adult BMI-values of 25–30  $kg/m^2$  for overweight and  $\geq 30$   $kg/m^2$  for obesity (25). Data on family characteristics comprised the number of sibs, and parental asthma. Living conditions included day care attendance, household crowding, pet ownership, bedroom carpeting, gas cooking, home dampness, living in a non-isolated house, limitations to ventilate, and household tobacco smoking. Household crowding was defined by bedroom sharing or less than one room per household member. Pet ownership referred to having a cat or dog 'ever', 'currently', or 'in the first 2 yrs of life'. Bedroom floor carpeting was defined as 'smooth' if no textile carpet present. Kitchen gas use addressed gas use for cooking or warm kitchen water supply. Home dampness was defined as moulds (outside the bathroom) or moist in the past 12 months. Limitation to ventilate the house was defined by a report of frequently feeling limited to ventilate because of stench, dust, or noise on a scale of three, i.e. 'mostly not', 'sometimes', and 'frequently'. Household smoking was defined by regular indoor smoking by the mother, father, or another person 'when the child was 0–2 yrs old', '2–4 yrs old', 'older than 4 yrs', and 'currently'. Apart from exposure to tobacco smoke in different periods of life, we also estimated the cumulative years of exposure by summing the duration of exposed age-periods, in which the first and last age-periods of exposure counted for half of the duration. For example, if for a 10-yr old child household smoking was reported at age 2–4, after age 4, and currently, cumulative tobacco smoke exposure years was estimated at 7 yrs ( $1 + (10-4)$ ). If there was not current household smoking, cumulative tobacco smoke exposure was estimated at 4 yrs ( $1 + ((10-4)/2)$ ).

#### Statistical analyses

We analyzed all data using logistic regression analysis in the SAS 9 statistical software package (SAS Institute, Cary, NC, USA). Because of the hierarchical sampling strategy (children within schools), we first assessed whether data of individual children were correlated per school by multilevel analyses using MLWin 2.02 (<http://www.cmm.bristol.ac.uk/MLwiN>). This showed no significant intra-class correlations per school, allowing further analyses to be performed by routine (one-level) analyses using the SAS 9 statistical software package (SAS Institute).

Prevalence rates of health outcomes were compared for the three levels of parental education using chi2-testing, and oneway ANOVA for  $FEV_1$ . Age and sex adjusted odds ratios and 95% confidence intervals were determined using logistic regression. For health outcomes that yielded a statistically significant association ( $p < 0.05$ ) each explanatory variable was included in the logistic regression model and evaluated the degree to which it changed the odds ratio in the direction of 1.0.

#### Results

Figure 1 summarizes data collection for the population. Of the 3262 eligible participants, data on parental education were obtained for 3213 children (mean age was 9.8 yrs, 51.1% girls). Atopy testing was performed in 1983 (61.7%) children with data on parental education of whom 1057 by SPT and 1682 by serum specific IgE. Parental education was similar for atopy testing by SPT or serum IgE. Atopy prevalence rates were similar for a positive SPT and serum specific IgE (respectively 28.1% and 27.6%). Permission for airway challenge testing was obtained for 1097 (57.7%) of the 1901 invited children. Test results of 197 children were excluded because baseline  $FEV_1 < 75\%$  predicted ( $n = 13$ ) or inability to perform satisfactory maneuvers ( $n = 100$ ). Another 100 tests were discarded because of tiredness or excessive cough.  $PD_{15}$  could not be assessed for 20 subjects due to an insufficient inhaled amount of HS, i.e. less than 23.0 g while not hyperresponsive. Participants and non-participants of atopy and airway challenge testing did not differ in parental education, and symptom prevalence rates ( $p > 0.10$ ).

Parental education was low in 30.6%, intermediate in 30.0%, and high in 39.4%. As shown in Table 1, wheeze prevalence rate decreased

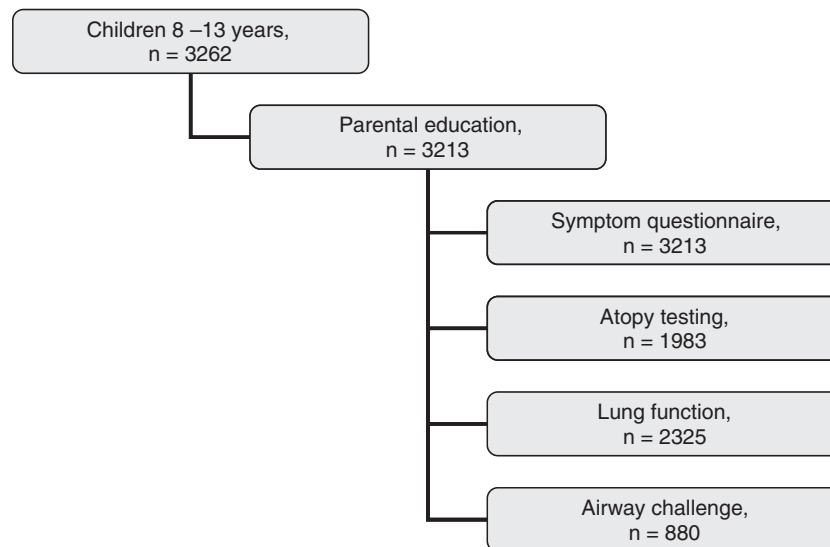


Fig. 1. Data collection and participation.

with parental education ( $p = 0.028$ ). In contrast, a positive trend was observed for atopic sensitization to indoor allergens ( $p = 0.022$ ). Prevalence rates for an itchy rash, AHR, and serum total IgE levels also increased with parental education, but without statistical significance ( $p > 0.10$ ).

Table 2 shows prevalence rates of studied explanatory factors by parental education. A positive trend with parental education was observed for breastfeeding, family size, living space in the house, and having attended a daycare centre. In contrast, children from highly educated parents less frequently were born preterm or had a low birth weight, less frequently were overweight or obese, exposed to household

tobacco smoke, had a cat or dog. No difference by parental education was observed for parental asthma, home dampness, living in a non-isolated house, and limitations to ventilate the house (all  $p > 0.10$ ).

Results of logistic regression analyses adjusted for age and gender (Table 3) are consistent with results presented in Table 1. Children of highly educated parents were more frequently sensitized to indoor allergens (OR 1.31, 95% CI 1.02; 1.69), and protected from wheeze (OR 0.77, 95% CI 0.61; 0.97). The odds ratio for AHR was higher than for atopic sensitization to indoor allergens, respectively 1.37 and 1.31, but did not reach statistical significance ( $p > 0.10$ ). This likely is due to the lower number of participants

Table 1. Percentage prevalence rates of child allergic and respiratory conditions by parental education

	All	Parental education			p (trend)
	%	Low (n = 982)	Intermediate (n = 966)	High (n = 1265)	
Ever asthma (n = 3179)	7.8	8.2	8.2	7.1	0.310
Wheeze (n = 3160)	15.7	17.2	16.7	13.8	0.028
Rhinitis (n = 3186)	24.4	23.7	25.2	24.3	0.770
Rhinoconjunctivitis (n = 3170)	8.5	8.8	8.4	8.4	0.724
Itchy rash (n = 3189)	15.2	13.9	15.1	16.1	0.148
Asthma medication (n = 3195)	5.2	5.6	5.5	4.6	0.264
Inhaled corticosteroid (n = 3195)	2.7	3.1	3.1	2.2	0.163
Atopy (n = 1983):					
Any allergen	29.2	28.3	26.4	31.9	0.106
Indoor allergen	23.1	21.2	20.9	26.1	0.022
Outdoor allergen	19.5	19.8	18.8	19.7	0.989
AHR (n = 880)	20.1	17.5	19.7	22.3	0.129
Mean FEV1, %predicted (s.d.) (n = 2325)	100.4 (11.4)	100.0 (11.4)	101.0 (11.7)	100.1 (11.1)	0.995



Table 2. Percentage prevalence rates of personal, family and living characteristics by parental education

	Parental education			p (trend)
	Low	Intermediate	High	
Premature birth	11.3	9.9	8.1	0.010
Low birth weight	14.2	12.1	10.1	0.003
Breastfeeding				
Any	49.4	65.3	76.0	<0.001
Longer than 3 months	22.0	31.6	45.0	<0.001
Overweight or obese	18.6	15.4	12.7	<0.001
Parental asthma				
Mother	8.1	5.7	6.7	0.249
Father	6.8	6.0	7.4	0.517
Sibs				
None	10.6	7.9	6.2	<0.001
Two or more	33.5	38.1	47.3	<0.001
No older sibs	47.2	47.9	45.7	0.451
Day care attendance at age 0-1	1.8	3.0	10.2	<0.001
Living space				
>1 person/room	14.6	12.9	8.2	<0.001
Child shares bedroom	14.6	12.2	14.1	0.761
Maternal smoking during pregnancy	40.5	29.6	17.8	< 0.001
Household smoking				
Current	69.6	58.3	42.2	<0.001
First 2 yrs of life	76.3	65.2	50.6	< 0.001
Years, mean (s.d.)	7.0 (4.5)	6.0 (4.8)	4.6 (4.8)	< 0.001
Pet owner				
Child age 0-2 yrs	53.7	47.9	40.3	<0.001
Current	53.7	46.0	39.3	<0.001
Smooth bedroom floor carpeting	38.5	39.7	46.9	<0.001
Kitchen gas use				
Cooking	83.0	80.9	80.4	0.130
Water-heater	23.2	14.0	10.5	<0.001
Home dampness	29.4	30.0	29.7	0.891
Limitations to ventilate	34.2	37.8	37.5	0.136
Non-isolated house	54.6	55.4	57.7	0.153

Table 3. Results of logistic regression analyses for parental education and child allergic conditions; odds ratios (95% confidence intervals) adjusted for age and sex

	Parental education		
	Low	Intermediate	High
Wheeze; n = 3179	1.00	0.96 (0.76; 1.22)	0.77 (0.61; 0.97)*
Ever asthma, n = 3160	1.00	1.00 (0.72; 1.30)	0.84 (0.62; 1.16)
Rhinitis; n = 3186	1.00	1.09 (0.69; 1.31)	1.04 (0.85; 1.26)
Rhinoconjunctivitis; n = 3170	1.00	0.95 (0.69; 1.31)	0.96 (0.71; 1.29)
Itchy rash; n = 3189	1.00	1.11 (0.86; 1.44)	1.21 (0.95; 1.53)
Atopy; n = 1983			
Any allergen	1.00	0.92 (0.71; 1.19)	1.18 (0.94; 1.50)
Indoor allergen	1.00	0.99 (0.74; 1.31)	1.31 (1.02; 1.69)*
Outdoor allergen	1.00	0.94 (0.70; 1.26)	0.99 (0.76; 1.29)
AHR; n = 880	1.00	1.17 (0.75; 1.84)	1.37 (0.92; 2.04)

\*p < 0.05.

compared with the other outcomes, which reduces statistical power. Relationships were similar for fathers' and mothers' education (Fig. 2).

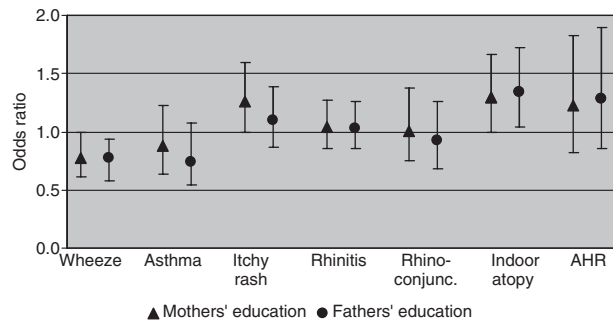


Fig. 2. Odds ratios for a high parental education and children's allergic and respiratory conditions, adjusted for age and sex.

To unravel the contra-intuitive finding of a positive association with atopic sensitization and a negative association with wheeze, we performed logistic regression analyses for atopic and non-atopic conditions separately using non-atopic children without symptoms as reference group (Table 4). The protective odds ratio for a high parental education was observed for non-atopic wheeze only, while no relationship with atopic wheeze was found. Similar results applied to rhinitis symptoms with a high parental education being protective for non-atopic rhinitis and no association for the atopic subtype.

Aiming at the explanation of observed differences in atopic sensitization and non-atopic symptoms by parental education, explanatory variables were included in the logistic regression models. For atopic sensitization, adjustment for none of the variables presented in Table 2 changed the odds ratio more than 10%. Table 5 shows results for models that decreased the protective odds ratio with 10%: OR  $\geq 0.72$  and OR  $\geq 0.77$  for respectively non-atopic wheeze and non-atopic rhinitis. For both outcomes, household smoking explained part of the protection among children of highly educated parents. The largest change in odds ratio was obtained for the number of years exposed to household smoking, i.e. from 0.65 to 0.81 for non-atopic wheeze and from 0.70 to 0.77 for non-atopic rhinitis, respectively. Inclusion of early life household smoking did not additionally change the odds ratio, but current household smoking further increased the odds ratio for non-atopic wheeze to 0.87. The higher rate of breastfeeding among highly educated parents also contributed to the protection from non-atopic wheeze. Inclusion of household smoking and breastfeeding in the model for non-atopic wheeze, completely explained the protection by a high parental education (OR 0.96, 95% CI 0.58; 1.57).

Table 4. Association of a high parental education with atopic and non-atopic symptoms, odds ratio (95% confidence interval) adjusted for age and sex

	Atopic		Non-atopic		Reference†
	N	OR (95% CI)	N	OR (95% CI)	N
Wheeze	165	0.89 (0.60;1.31)	143	0.65 (0.43;0.99)*	1239
Rhinitis	256	1.14 (0.82;1.59)	249	0.70 (0.50;0.98)*	1142
Rhinoconjunctivitis	137	1.06 (0.69;1.62)	39	0.64 (0.30;1.37)	1347
Itchy rash	135	1.01 (0.63;1.63)	166	1.28 (0.83;1.96)	1228

\*p &lt; 0.05.

†Non-atopic children without the symptom of the regression model.

## Discussion

Children of highly educated parents were more frequently sensitized to common indoor allergens, but protected from wheeze though only for non-atopic and not for atopic wheeze. Similar results were observed for rhinitis. The lower rate of household smoking in highly educated families yielded the largest explanation for both the protection from non-atopic wheeze and rhinitis.

It is attractive to ascribe the higher rate of atopy in children of highly educated parents to excess 'hygiene' in early life which has been hypothesized to shift the immune response towards an allergic one (26, 27). In this study, however, none of the studied environmental factors explained the association of a high parental education and atopy, although most of them were reported least frequently by highest educated families.

We neither confirmed a role for family predisposition as found by others (19–21) Parental asthma was reported equally among classes of educational level, and did not influence the relationship with atopic sensitization.

For wheeze and rhinitis, the association with parental education depended on the presence of atopy. While atopic wheeze and rhinitis did not

show a socioeconomic gradient, non-atopic wheeze and rhinitis occurred less frequently in children of highly educated parents. We did not find an association between parental education and AHR and rhinoconjunctivitis. This is consistent with the lack of an association with atopic wheeze and rhinitis, since AHR and rhinoconjunctivitis are strongly related to atopy.

Our results clearly show the relevance of distinguishing between atopic and non-atopic asthma. The inconsistent findings on socioeconomic position and asthma in previous studies may at least partly be due to lack of this distinction. In our population, almost half of the children that reported wheeze were non-atopic (46%), which is high compared to other studies. This may explain our observation of an association between parental education and wheeze when taking together the atopic and non-atopic phenotype.

The lower rate of household smoking and higher rate of breastfeeding among highly educated families significantly explained the protection from non-atopic wheeze. Highly educated parents less frequently reported other risk factors including low birth weight, child overweight or obesity, and gas cooking. Though, neither of these contributed to the explanation of the protection. Interestingly, we observed that lifetime exposure and current exposure to tobacco smoke independently explained part of the protection from non-atopic wheeze in children of highly educated parents which suggests both chronic and acute mechanisms. However, our results need to be interpreted cautiously. Data on smoking were collected retrospectively, and our estimates of smoking years lack precision. Birth cohort studies will allow profound study of trajectories of environmental tobacco smoke exposure over time.

We can only speculate on the mechanism of our observations. Likely, children of lowly educated families are more susceptible to viral infections due to environmental tobacco smoke as a predisposing factor, while protective factors

Table 5. Odds ratio's and 95% confidence intervals for the relationship of a high parental education with non-atopic symptoms

	Non-atopic wheeze	Non-atopic rhinitis
Model 1	0.65 (0.43; 0.99)	0.70 (0.50; 0.98)
Model 2A	0.78 (0.50; 1.23)	∞
Model 2B	0.79 (0.51; 1.33)	∞
Model 2C	0.81 (0.50; 1.31)	0.77 (0.52; 1.13)
Model 2D	0.87 (0.53; 1.41)	∞
Model 3	0.73 (0.47; 1.13)	∞
Model 4	0.96 (0.58; 1.57)	∞

∞ not presented: change in odds ratio &lt; 10%.

Model 1: adjusted for age and sex, Model 2A: model 1 + household smoking in the first 2 yrs of life, Model 2B: model 1 + current household smoking, Model 2C: model 1 + years exposed to household smoking, Model 2D: model 2B + model 2C, Model 3: model 1 + breastfeeding, Model 4: model 2D + model 3.

(e.g. breastfeeding) are less common in lowly educated families. Additionally, environmental tobacco smoke exposure may contribute to more severe, therapy-resistant asthma (28), due to neutrophilic inflammation (29), and exacerbation of allergic responses (30, 31).

Our study results suggest that a great deal of the burden of non-atopic wheeze in children of lowly educated parents can be prevented by increasing breastfeeding and reducing household smoking. One might doubt the generalizability of our results since the contribution of an explanatory factor depends on its distribution in the population. However, in most industrialized countries household smoking is more common in low socioeconomic families (6) which adds to the generalizability of our findings.

Strengths of our study are the large sample size, extensive data collection, and inclusion of objective markers of allergic disease. The major limitation of our study is that only a part of the population participated in atopy and airway challenge testing. This limits comparison of the results for the different outcomes under study, in particular for AHR. A second limitation is our definition of socioeconomic position, for which parental education was the only available indicator. We made an attempt to meet this shortcoming by using the highest educational level, assuming this to represent family income most closely. Finally, the cross-sectional design limits causal inference, and does not account for changes in socioeconomic position and symptoms. So far, only two follow-up studies did evaluate the relationship between socioeconomic position and childhood allergic disease (32, 33). The lack of well-designed studies on this topic shows that research on social factors in asthma epidemiology is still in its infancy.

In summary, a high parental education is associated with a higher risk of atopic sensitization though not with atopic symptoms. In contrast, children of highly educated parents are protected from non-atopic respiratory symptoms for which a lower rate of household tobacco smoking gives the largest explanation. We conclude that a reduction of non-atopic respiratory symptoms in children of lowly educated parents may be achieved by successful prevention of household smoking in these families.

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